# Correspondence

## Are Serum Cytokines Sensitive and Specific Enough to Prognosticate in Aspergillosis?

Chai et al [1] are to be commended for their admirable effort to find associations between some (IL-6, IL-8, IL-10, INF-8, and C-reactive protein) but not all serum cytokines and the clinical response (at 12 weeks) and outcome (mortality at day 84) in patients with invasive aspergillosis (IA). Because no IA-attributable mortality was analyzed, the similarity in cytokine profiles with nonresponders and nonsurvivors is reassuring; several competing causes of death exist in severely immunosuppressed hosts who develop IA.

However, these interesting data do not address the issue of whether serum cytokine level changes are inherently linked to the natural history of IA (progression or not) per se and not to the underlying disease. As up to 74% of patients in the cohort analyzed had hematologic malignancy, and because information about remission rates and neutropenia status (eg, recovery or not in cytopenic patients) in responders or not is not provided, a question arises: are these cytokine changes merely a sophisticated marker to describe the evolution of underlying hematologic disease? For example, Kornblau et al [2] recently described that there are specific serum cytokine signatures (including IL-8) that impact leukemia-related survival, independent of infections. The possible influence of underlying disease and neutrophil count is reflected by the contrasting findings of an earlier, smaller study by Roilides et al [3] in 7 nonneutropenic patients with IA. Furthermore, because up to 10% of patients with invasive mycoses have another infection (bacterial or fungal) at autopsy [4], it might be premature to ascribe all these cytokine changes to IA alone. Only measurement of a wide spectrum of serum cytokines and chemokines in a well-matched control group (same underlying disease but without IA) and careful association of serum cytokine levels with the quality of hematologic remission, cytogenetic abnormalities, coinfections, and grade of mucositis could address specificity issues convincingly.

Furthermore, issues about sensitivity remain. Levels of cytokines would be significantly different (lower or higher) depending on whether measurements were done in serum or plasma samples [5]. Perhaps plasma is a better platform to evaluate the association of cytokine kinetics with IA outcome. Finally, it is uncertain whether serum cytokine levels mirror the pathophysiology of a primarily sinopulmonary infection such as IA. Up to 90% of patients in the study by Chai et al [1] had pulmonary IA. It is unclear how many of these cases were limited to a single lung nodule, compared with extensive pulmonary disease, or sequestration and angioinvasive process, both factors that would influence the spill over of cytokines from the site of primary infection (lungs) to systemic (bloodstream) compartment.

Beyond the artificiality of animal models of IA, human IA is a true opportunistic infection that occurs in complex clinical scenarios that could influence, in multiple ways, the proinflammatory signatures. This is an important and complicated area of research that requires prospective, carefully controlled, prospective, large sample sets and casting the net widely by measuring cytokines and/or chemokines to gain more insight on the validity of cytokines as surrogate, early prognostic markers in IA.

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### References

1. Chai LA, Netea MG, Teerenstra S, et al. Early proinflammatory cytokines and C-reactive protein trends as predictors of outcome in invasive Aspergillosis. J Infect Dis **2010**; 202:1454–62.
2. Kornblau SM, McCue D, Singh N, Wenjing C, Estrov Z, Coombes KR. Recurrent expression signatures of cytokines and chemokines are present and are independently prognostic in acute myelogenous leukemia and myelodysplasia. Blood **2010**; 117:780–7.
3. Roilides E, Sein T, Roden M, Schaufele RL, Walsh TJ. Elevated serum concentrations of interleukin-10 in nonneutropenic patients with invasive aspergillosis. J Infect Dis **2001**; 183:518–20.
4. Chamilos G, Luna M, Lewis RE, et al. Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989–2003). Haematologica **006**; 91:986–9.
5. Stroncek D, Slezak S, Khuu H, et al. Proteomic signature of myeloproliferation and neutrophilia: analysis of serum and plasma from healthy subjects given granulocyte colony-stimulating factor. Exp Hematol **2005**; 33:1109–7.

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